blood pressure reduction was considered. Of the 12 patients who lost 5 pounds or more, one-half evidenced a temporal relationship. Time curves did not coincide in the others. Upon discontinuation of the drug, weight was often regained more slowly than blood pressure was reelevated. In approximately two-thirds of the patients, change in stool flora coincided with the hypotensive effect. However, in one of these patients, a second course of furazolidone therapy failed to show such relationship. Consequently, it is not yet possible to draw conclusions regarding possible mechanism of hypotensive action.

Dosage required to lower blood pressure optimally in this study was considerably higher than that which has been recommended for enteric antibacterial therapy. At such high doses, the adverse effects, most frequently gastrointestinal in nature, definitely limit application of the drug in treatment of hypertension. Development of a refractory state to the vasodepressor action is a problem which has not been solved by increasing the dose. However, furazolidone may represent a new point of departure from which other derivatives may retain potent antihypertensive action dissociated from the aforementioned limitations.

Conclusions. Furazolidone in adequate dosage exerts a significant hypotensive action. The exact mechanism whereby this occurs remains obscure. Frequency and severity of adverse effects and development of a refractory state limit application of the drug in treatment of patients with hypertension. It is to be hoped that derivatives may dissociate the hypotensive from the unwanted effects.

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Effect of Antihistaminic and Antiserotonin Drugs on Vascular Responses to *E. coli* Endotoxin in the Cat.* (24622)

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Devices by which endotoxin causes shock and death are only partly understood. The resemblance of its early vascular effects in certain species(1) to changes seen in anaphylaxis (2) has suggested that there may be certain mechanisms common to both situations. Since histamine and 5-HT (5-hydroxytryptamine) are known to be released in anaphylaxis(3) it seemed possible that they may also be set free in reactions to endotoxin and that antihistaminic and antiserotonin drugs might therefore block some effects of endotoxin. Chlorpromazine, which has both antihistaminic and adrenergic blocking activity(4) has been shown to protect mice against lethal effects of endotoxin(5). Dibenzyline has also been found to have a protective effect(6,7). In the present study, a combination of dibenamine and pyrilamine blocked the *immediate* systemic hypotensive effect of small doses of endotoxin in cats.

Methods. In the cat, endotoxin causes a sharp rise of PAP (Pulmonary artery pressure) and of total pulmonary vascular resistance. This is followed by a decline in BP (systemic arterial blood pressure) from which there is usually a temporary recovery(8). Cats were anesthetized with intraperitoneally injected sodium pentobarbital (35 mg/kg). After cannulation of the trachea and carotid artery, the chest was opened to permit insertion of a polyethylene catheter into the pulmonary artery. The PAP and BP were meas-

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TABLE Ia. Responses to Histamine (20 μg/kg) before and after an Antihistaminic.

Antihistaminic and dose	BP change (mm Hg) Before	BP change (mm Hg) After	PAP change (mm Hg) Before	PAP change (mm Hg) After
Tripellenamine, 2.5 mg/kg, and diphenhydramine, 2.5 mg/kg	−65	−35	− 2	
Chloropropheupyridamine maleate, 2 mg/kg	−22	−18	+ 3	− 1
Promethazine				
25 mg/kg	−40	−20	+ 8	+5
20 "	−33	−31	+ 1	+1
Pyrilamine, 5 mg/kg	−51	− 7	+16	+1
Idem	−60	−17	+12	− 2
"	−33	−34	+13	− 2
"	−85	−40	+12	+2
"	− 5	−30	+15	+3

ured and recorded with Statham strain gauges and a Sanborn 2-channel recorder. The purified endotoxin from *E. coli* was prepared by a modified Boivin technic as described by Spink and Anderson(9). 5 mg/kg of this preparation was fatal to 7 of 8 cats when given intravenously.‡ A different cat was used for each test with endotoxin. All injections were made through a polyethylene catheter which had been inserted in the external jugular vein. Dilutions of histamine and 5-HT in 5% dextrose solution were made afresh each day. All doses are stated in terms of the base. Dibenamine from a stock solution in acidified propylene glycol and ethanol was diluted with normal saline immediately prior to injection. LSD (lysergic acid diethylamide) was injected as supplied,§ as was the commercially obtained pyrilamine. To allow time for the blocking drugs to become effective, injection of endotoxin was delayed for an hour after their administration.

Results. The effect of several antihistaminic drugs on BP and PAP responses to a standard dose of histamine is shown in Table Ia. The effects of dibenamine and LSD on pressure responses to 5-HT are shown in Table Ib. The blocking action of these agents against histamine and 5-HT was unpredictable and incomplete. It was therefore decided to use only 0.05 mg/kg of endotoxin, a dose 1/100 that used in dog studies reported from this laboratory. This amount of endotoxin was sufficient to consistently cause a clearly observable effect.

The results for both control and pretreated cats are shown in Table II. The most clear-cut protection was seen from a combination of dibenamine and pyrilamine. The BP was not significantly affected by endotoxin in any of 5 cats so pretreated. Fig. 1 contrasts the record obtained from such an experiment to that obtained from a control animal. The findings in the 15 control cats make it unlikely that the lack of a blood pressure fall in the pretreated animals was related to their lower initial pressure. The initial BP in the control cats ranged from 75 to 155. In these 2 animals BP fell 45 and 0 mm Hg respectively. The correlation coefficient between the initial BP of the control cats and the fall in pressure after endotoxin was only +.128 ($t = .465$, $P > .50$).

Dibenamine alone was effective in all but one of 5 trials and its average effectiveness was significant at the .05 level. Pyrilamine alone had no significant protective action. Neither LSD by itself nor LSD with pyrilamine gave significant protection in groups of 4 cats. When data for these 2 groups were pooled however, degree of protection against acute hypotensive effects of endotoxin became statistically significant at the .02 level. The effect of a large dose of endotoxin (5 mg/kg) was unaltered by any of the agents or combinations shown. The effect of these various

TABLE Ib. Responses to 5-HT (20 μg/kg) before and after Blocking Agent.

Blocking drug and dose	BP change (mm Hg) Before	BP change (mm Hg) After	PAP change (mm Hg) Before	PAP change (mm Hg) After
Dibenamine, 15 mg/kg	−38	−15	+ 6	+1
Idem	−15	−13	+27	0
"	−45	−20	+ 2	+1
LSD, .5 mg/kg	−25	−20	+ 6	+5
Idem	−35	−20	+ 6	−2
"	−25	−13	+ 9	+3
"	−30	−35	+ 4	− 5

‡ Endotoxin was made available through the courtesy of Dr. Wesley W. Spink, Univ. of Minnesota.

§ LSD was provided in ampoules containing 0.1 mg/ml of LSD through courtesy of Dr. R. Bircher of Sandoz Pharmaceuticals.

TABLE II. Responses to Endotoxin with and without Blocking Drugs.

No. cats	Drug before endotoxin	BP BP change ⌐ mm Hg ¬		% change BP	P	PAP PAP change ⌐ mm Hg ¬		% change PAP	P
15	None (control)	112	−50	−45.0 ± 9.0*		16.6	+12	+73 ±17 *	
5	Dibenamine, 15 mg/kg, and pyrilamine, 5 mg/kg	78	+ 2	+ 2.8 ± 3.1	<.01	11.2	+ 3	+26.8 ±10.3	>.10
5	Dibenamine, 15 mg/kg	66	− 9	−14.8 ± 8.5	<.05	14.2	+ 6	+49 ±34.2	>.10
5	Pyrilamine, 5 "	97	−21	−17.6 ±15	>.10	17.4	+ 7	+52 ±23.5	>.10
4	LSD alone, .5 "	65	− 6	− 8.0 ± 5.1	>.05	20.0	+ 9.7	+48.7 ±15.8	>.10
4	LSD, .5 mg/kg, and pyrilamine, 5 mg/kg	68	− 8	−11.6 ± 2.3	>.05	19.0	+ 2.5	+15.4 ± 6.9	>.05
8	LSD, .5 mg/kg, alone or plus pyrilamine, 5 mg/kg	67	− 7	− 9.9 ± 3.21	<.02	20.0	+ 6.1	+32.0 ±10.4	>.05

* ± S.E.

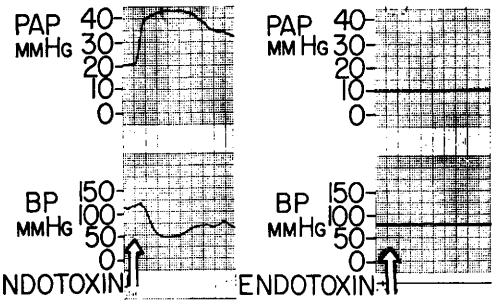

FIG. 1. Left side of illustration shows effects of endotoxin (.05 mg/kg) on pulmonary artery pressure (PAP) and arterial pressure (BP). Right side shows lack of effect of endotoxin in a cat which had received pyrilamine (5 mg/kg) and dibenamine (15 mg/kg). Heavy time lines are 2.5 sec. apart.

drugs on PAP responses to endotoxin was not statistically significant.

Tetraethylammoniumchloride (5 mg/kg) was ineffective in 3 cats. BAS (benzyl analogue of serotinin, 1 mg/kg)‖ was administered by stomach tube to 2 cats for 3 successive days. The effect of endotoxin given on the third day was unaltered.

Discussion. These data indicate that prior administration of antihistaminic and antiserotonin drugs can prevent acute hypotensive effects of small doses on endotoxin in cats. It is possible that in a larger number of cats partial protection could be shown for pyrilamine or LSD alone. Tetraethylammoniumchloride and BAS had no effect on the acute response to endotoxin in 3 and 2 trials respectively.

Previous workers have shown that dibenzyline and chlorpromazine improve *survival* rate of mice given endotoxin(5,6). Similar results have been shown for other forms of shock (10). Boquet and Izard found that dibenamine greatly diminished vasoconstriction produced by endotoxin in the rabbit's ear(11). Lillehei and MacLean(7) have recently shown that either dibenzyline or chlorpromazine greatly improve survival rate in dogs given endotoxin. Initial BP response was not affected. Our data concern the initial *acute* circulatory response in cats. The results are compatible with the thesis that histamine and 5-HT are released in the initial stages of the endotoxin reaction. Although there was no blocking of the response to *large* doses of endotoxin, neither was there blocking of the responses to large doses of histamine or 5-HT. It is, of course, quite possible that the effect was on other vasoactive amines or was a nonspecific action against totally different agents. It is improbable that epinephrine blockade alone is a factor, since the early endotoxin response is so different from that seen after epinephrine.

Despite the statistically insignificant effect of these drugs on the PAP response to endotoxin, it is likely that the pulmonary vascular constriction was sufficiently abated that the left ventricular output and hence the BP were not significantly affected by the endotoxin.

Summary. Pretreatment with dibenamine and pyrilamine, dibenamine alone, or LSD with or without pyrilamine was found to diminish or prevent the acute hypotensive response of the cat to small doses of endotoxin.

‖ BAS and instructions for its administration were kindly supplied by Dr. D. W. Woolley, Rockefeller Inst.

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Detection and Isolation of Formiminoglutamic Acid from Urine in Folic Acid Deficiency in Humans.*† (24623)

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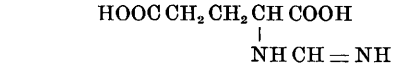
Silverman and coworkers(1) found that rats on folic acid (FA) deficient diet excreted in the urine a compound which was converted to glutamic acid when heated or exposed to alkali. Excretion of the glutamate precursor was associated with severity of FA deficiency (1) and increased by supplementing the diet with histidine(2). Subsequent chemical evidence(3) indicated that the glutamate precursor was N-formiminoglutamic acid (formamidinoglutaric acid):



Formiminoglutamic acid (FIGLU)

That a metabolic relationship between FA and FIGLU exists has become clearer with recent enzyme studies. Thus it has been shown that FIGLU may arise from degradation of histidine by liver homogenates and *Pseudomonas* extracts(4) and that tetrahydrofolic acid (THFA) functions in certain mammalian enzyme systems(5,6) as acceptor of formimino group of FIGLU giving formimino-THFA(6) and glutamic acid. Our study was undertaken to determine if FIGLU might be excreted in FA deficiency in man. Such findings would support concept that FA functions in formimino group transfer, and suggest detection of FIGLU in human urine be considered as a diagnostic tool for folic acid deficiency in man. Preliminary findings have previously been reported by us(7,8,9).

Methods. Twelve children with acute leukemia receiving various types of chemotherapy, one woman with macrocytic anemia of pregnancy and 5 normal subjects were studied. Highlights of clinical findings in addition to data in Table I, are: Subj. 1: A.B. Acute myeloblastic leukemia associated with mongolism, no previous antileukemic therapy, in clinical and hematologic relapse, blood WBC 28,600 mm^3, when urine collected; Subj. 2: S.M. Subacute lymphatic leukemia, no response to previous 6-mercaptopurine (Purinethal)® or steroid therapy, in clinical and hematological

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